-- 50. The method of claim 26 wherein said cells obtained in (a) are derived from human neural tissue. --

-- 51. The method of claim 26 wherein said mammalian neural tissue in (a) is selected from the group consisting of tissue obtained from cerebral cortex tissue, cerebellum tissue, midbrain tissue, brainstem tissue, spinal cord tissue, ventricular tissue, frontal lobe tissue, conus medullaris tissue, hypothalamus tissue, and combinations thereof. --

REMARKS

Amendment to Title

In view if the restriction requirement in this application, the title has been amended to more specifically identify the elected subject matter.

Amendments to Specification

The specification is amended in various places to correct grammatical/typographical errors and to place "degrees" symbols in the superscript position. Pages 30 and 32 are amended to provide the complete names for the commonly used acronyms GABA and BDNF. Amendments have also made to clarify when trademarked terms are used. Page 83 is amended to refer to the correct Example which discloses the procedure referred to. Page 100 is amended to correct an obvious error. Support for this amendment is evident at line 17 of page 100.

Amendments to the Claims:

Claim 26 is amended to more clearly and succinctly define the applicants' invention.

Support for new claims 32 to 50 exists throughout the specification and at the following specific locations:

Claims 32 to 35: page 26, lines 5 to 18;

Claim 36: page 56 lines 4 to 22;
Claim 37: page 57, lines 19 to 25.
Claim 38: page 57, line 32 to page 58, line 2.
Claims 39 and 40: page 29, line 6 to page 30 line 7;
Claim 41 to 46: Table III on page 102;
Claim 47: page 98, line 30;
Claims 48 to 50: page 21, lines 9 to 13; and
Claim 51: page 20 line 25 to page 21, line 16.

The new claims further define the subject matter elected in this application. Accordingly, examination of the new claims in this application is believed to be proper.

Objection to the Drawings:

The draftsperson's objection to the drawings is noted. Applicants intend to address this objection upon indication of allowable subject matter.

Information Disclosure

An information disclosure statement and accompanying form PTO form 1449 are filed herewith.

Rejections Under 35 U.S.C. § 112

The Examiner rejected claims 26 and 27 under § 112, 1st paragraph as not being enabled by the specification. The Examiner states that the claims "are broad in that they encompass all neural stem cell progeny and it is not apparent from the specification that any and all neural stem cell progeny can be obtained and transplanted as claimed." The specification discloses methods for proliferating multipotent neural stem cells which give rise to daughter multipotent neural stem cells, and all three of the differentiated neural cell types: astrocytes, oligodendrocytes and neurons. Using

immunocytochemistry methods it has been shown that all three of these cell types can be obtained by the growth factor-induced *in vitro* proliferation of multipotent neural stem cells (see caption to Figure 2 on page 18). It has also been shown, that using the methods disclosed in the specification, that the neural stem cell progeny includes daughter multipotent neural stem cells, as evidenced by their ability to produce the three differentiated neural cell types in subsequent culture steps and the self-maintenance capacity of the cells (e.g. see Example 20 on page 72 where it is disclosed that neurospheres were passaged weekly for 35 weeks). Thus, the Examiner statement that "it is not apparent from the specification that any and all neural stem cell progeny can be obtained" is puzzling. The specification provides more than ample direction on how one can obtain multipotent neural stem cell progeny.

The Examiner's § 112, 1st ¶ rejection is also based on the assertion that "it is not apparent from the specification" that neural stem cell progeny can be "transplanted as claimed." However, the specification shows that neural stem cell progeny can be successfully transplanted into animals, where they survive, migrate to appropriate locations within the host tissue, and form appropriate neural connections with neighboring cells. The ability of transplanted neurons to restore function and alleviate symptoms of neurological disorders is well-document in the art (for example see p. 6 of the specification, lines 13-18; see also Lindvall *et al.* "Grafts of Fetal Dopamine neurons Survive and Improve Motor Function in Parkinson's Disease" Science, vol. 247 ¶. 574-577, cited as reference no. 38 on the 1449 form filed herewith). In Example 45 of the specification, beginning on page 96, there is detailed discussion of the transplantation of neural stem cell progeny into various animal models of various disease. Successful integration of the neural stem cell progeny into the CNS of the animal models is shown. For example, on page 100, lines 8-19, neural stem cell progeny transplanted into rats having lesions (i.e. regions of damaged or lost neurons) in the hippocampal region, survive and form new neurons in the lesioned area.

Additionally, Example 15, beginning on page 68 of the specification, describes experiments which have been performed that show that when myelin deficient rats are injected with the progeny of multipotent neural stem cells, patches of myelin form, indicating that the neural stem cell progeny are capable of differentiating into oligodendrocytes and forming myelin *in vivo*. Thus, while multipotent neural stem cell progeny are capable of differentiating into neurons and astrocytes (as evidenced throughout the specification), as well as oligodendrocytes, these experiments show that at least some of the neural stem cell progeny, when transplanted adjacent areas of demyelinated neurons *in vivo*, will appropriately differentiate into oligodendrocytes and form myelin around the neurons.

Thus, clearly the specification enables one of ordinary skill in the art to obtain and transplant multipotent neural stem cell progeny.

Concerning the Examiner's remark that the claims "read on any transplantation site" (p. 3, middle ¶), numerous possible transplantation sites are disclosed in the specification (e.g. see Tables III and IV on pages 102 and 103). Accordingly, a sufficient number of embodiments of the claimed invention have been provided to enable the full scope of the claim.

The Examiner commented at the top of page 4 of the office action that page 17 of the specification states that "the claimed invention is directed towards a method for treating neurodegenerative diseases". The present claims do not refer to treatments of neurodegenerative disease, but rather methods of transplanting neural stem cell progeny. As neural stem cells can be induced to proliferate *in vitro* using applicants' methods, they are amenable to genetic modification, and thus can be genetically modified to express biological factors that would have use in treatments not necessarily limited to neurodegenerative diseases. This would have been immediately apparent to one of ordinary skill in the art at the time of the invention upon reading Applicants' disclosure. For example, at the time of the invention, the use of genetically modified encapsulated cells for delivering a variety of

needed biological factors to animals was widely known in the art. Thus, one of ordinary skill in the art, in view of the teachings of the specification, would know that encapsulation procedures could be used for neural stem cell progeny. Attached as Appendix B is U.S. Pat. No. 5,550,050, to Holland *et al.*, which discloses that neural stem cells are a preferred source of cells for encapsulation (see col. 8, lines 49 to 59).

The Examiner's remarks beginning on page 4 of the Office Action seem to be directed to whether sufficient evidence is provided in the specification to support a claim to any therapeutic effect for the treatment of neurodegenerative diseases. Thus, it appears that the Examiner is doubting whether a credible utility for the claimed invention has been shown. The Examiner acknowledges that myelin formed in the demyelination rat model discussed in Example 15, but stated that "it is not clear that the results from this experiment are indicative of any therapeutic effect." Myelin is a cellular sheath, formed by glial cells, that surrounds axons and axonal processes. The primary function of the myelin sheath is to facilitate conduction of the nerve action potential. In the absence of myelin, the propagation of the action potential is greatly reduced because ions, which carry the flow of current across the length of the axon, are free to diffuse across the axon membrane. Thus, the mere formation of myelin around a once demyelinated axon achieves a benefit by insulating the axon. Accordingly, a specific and credible utility of the claimed invention has been demonstrated. Under the criteria set forth in the "PTO Examination Guidelines on Utility Requirement", it is believed that the Examiner's rejection under § 112, 1st ¶ should be withdrawn.

The Examiner additionally states that "the specification and the prior art lack guidance on several parameters involving the transplantation of neural stem cell progeny..." including "...amounts of cells to be administered... sites for transplantation, requirements for repetitive transplantation and ways of measuring that a therapeutic effect has been achieved." (p. 5, middle of

page). However, this is untrue. The specification and prior art provide ample guidance in this regard. On page 38, lines 25 to 30, the specification directs the reader to several references that are available which detail various transplantation methods. The specification also provides examples of how transplantation would be performed in humans (see e.g. 14 on page 67), and provides working examples of how transplantation procedures can be performed on animal models (see Examples 15, and 45). There is disclosure concerning the numbers of cells transplanted in both the prior art, and the examples in the specification (e.g. p. 69, lines 10-11; p. 97, lines 5-26). There is also disclosure concerning the sites for transplantation (e.g. p. 38, lines 20-22; p. 40, lines 20-23; p. 69, lines 11-13; p. 98, lines 27-30; p. 99, lines 22-23). Moreover, one of ordinary skill in the art would be capable of ascertaining suitable sites for transplantation. With regards to ways of measuring whether any therapeutic effect has been achieved, such as various tests for cognitive ability, improvement in motor control, improvement in axon potential, etc, this information is readily available to those of ordinary skill in the art that need not be detailed in the specification. As has been stated by the Federal Circuit, "A patent need not teach, and preferably omits, what is well known in the art". Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986). See also M.P.E.P. §2164.01 and Spectra Physics, Inc. v. Coherent, Inc 3 USPQ 2d 1737 (Fed. Cir. 1987).

Regarding the Examiner's concern that the specification does not disclose "requirements for repetitive transplantation", this is something that would be ascertained in the course of clinical evaluations, or more likely, on a patient-by-patient basis. Applicants are not required to submit such data to establish patentability of a claimed invention (see MPEP § 2107.02 and cases cited therein).

At the bottom of page 5 of the office action, the Examiner relies on a review article by Emerich *et al.* for the proposition that the art of cell transplantation for the treatment of neurodegenerative disorders is

"unpredictable" (p. 5, last sentence).[1] The Examiner states that the article reports that "neural transplants do not necessarily produce behavioral recovery and in some cases have either no beneficial effects, magnify existing behavioral abnormalities or even produce a unique constellation of deficits. Firstly, Applicants cannot find where in the article it is stated that such procedures are "unpredictable". In contrast, the first sentence of the Abstract states that "Considerable evidence suggests that transplantation of fetal neural tissue ameliorates the behavioral deficits observed in a variety of animal models of CNS disorders." The review article reports the "multitude of positive results in animals" (p. 401, col. 2). Thus, this paper strongly supports the position that it is widely accepted by those skilled in the art that transplantation of neural cells is beneficial in the treatment of CNS disorders.

With regards to the Examiner's reliance on Emerich *et al.* for the proposition that neural cell transplantation is not entirely efficacious or safe, Applicants recognize that, as with most therapies, transplantation using neural cells has not been developed to the point where it is 100% effective and 100% safe. However, the PTO Examination Guidelines on Utility Requirement state that Patent Office personnel should not "require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans and that "these general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder." (60 FR 36263, p.300). The Guidelines further state that "it is improper for Office personnel to request evidence of safety in the treatment of human, or regarding the *degree* of effectiveness." (Guidelines, p. 308, col. 2; emphasis in original) and that this is the province of other government agencies, not the Patent Office.

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[1] In support of the § 112 rejection, several times the Examiner quoted portions of or referred to teachings in the cited references, but not once identified the location of the text relied upon. In this regard, the Examiner's attention is drawn to M.P.E.P. § 706.02 (j) which states that "it is preferable to provide references to the column or page and line numbers where a reference purportedly provides a relevant teaching." Doing this would be very helpful and time-saving to the applicants.

Thus, while the Emerich *et al.* paper reports that "In contrast to the multitude of positive results in animals, a number of other studies using animal models have reported either minimal or no beneficial effects of neural transplants on the behavioral deficits seen following brain injury", this is insufficient to support the Examiner's position that applicants' claimed invention lacks any therapeutic utility, and hence, that the claims do not meet the requirements of § 112.

As an aside, the Examiner's reliance on Emerich *et al.* for reporting that "pharmacological strategy on increasing the striatal dopamine levels by administration of L-dopa has met with limited long term success and may even result in deleterious side effects" is misplaced. This passage in Emerich *et al.* does not concern transplantation of dopamine-releasing cells, but instead concerns "pharmacological strategy", i.e. the administration of drugs such as L-dopa to the Parkinson's patient.

With regards to claim 27, which is directed to *ex vivo* gene therapy, the Examiner relies on Orkin *et al.* and Friedmann *et al.* for showing that the use of gene therapy for treatment of neurological disorders is unpredictable, and that therefore, undue experimentation would be needed to practice the claimed invention. In the "undue experimentation" analysis, several factors are considered, including the breadth of the claims. Applicants claimed invention is directed to the transplantation of genetically modified neural stem cell progeny. While the Orkin Report identifies several of the shortcomings of current gene therapy protocols, it is very general and is not directed specifically to gene therapy using neural cells nor is it directed specifically to *ex vivo* genetic modification, as required by the claimed invention. Therefore, the Orkin Report does not seem particularly relevant.

Several studies have shown the therapeutic benefits of transplantation of neural cells for the treatment of neurological disorders. For example, patients with Parkinson's Disease who received implants of neural tissue received a long-term clinical benefit. (see specification, p. 10, lines 18 to 28).

While such treatments are not without their shortcomings, as recognized by the Applicants' on page 10, line 29 to page 12, line 11 of the specification, it does not mean that these methods lack any therapeutic utility. Moreover, applicants' methods improve upon these prior art methods by providing a source of neural cells that can be easily induced to proliferate *in vitro* and thus become readily amenable to genetic modification. This is recognized in the Friedmann paper, which was cited by the Examiner, on page 212, col. 2 wherein it is stated that "precursor CNS cells or 'stem' cells, can be genetically modified and grafted to an injured or diseased CNS to replace an aberrant, injured or degenerating neural function." Friedmann also reports that such genetically modified cells can "give rise to developmentally appropriate structures after implantation" and express a transgene "for very long periods in the fully developed CNS."

For the above reasons, the Examiner's rejection under § 112, 1st paragraph, should be withdrawn.

Rejections Under 35 U.S.C. § 102

The Examiner cites Lubetzki (1990) for teaching a method of transplanting neural stem cell progeny. However, in contrast to the Examiner's characterization, this reference is concerned with transfection of enriched (80-90% pure) oligodendrocyte cultures, which are differentiated glial cells, and enriched (70-80% pure) O-2A cell cultures (see discussion of "cell cultures" on p. 67 of Lubetzki). Oligodendrocytes are differentiated glial cells, and O-2A cells are committed glial progenitor cells. The distinctions between differentiated glial cells and committed glial progenitor cells are discussed on page 19, line 26, to page 20, line 11 of the specification.

To further assist the Examiner in understanding the distinctions between the claimed invention and the prior art, attached as Appendix A is a diagram that illustrates the Applicants' invention.

Referring to the diagram, a multipotent neural stem cell is depicted as an X within a circle. In the presence of a growth factor, the multipotent neural stem cell proliferates **(A)** to form a cluster of daughter cells termed a "neurosphere." As indicated by the key of the diagram, the neurosphere contains daughter multipotent neural stem cells and daughter committed progenitor cells (depicted as a dot within a circle). Collectively, the cells of a neurosphere are termed "multipotent neural stem cell progeny", as indeed they are derived from a single multipotent neural stem cell. This proliferation scheme is referred to as "asymmetrical division", a known stem cell characteristic. The cells of a neurosphere can be dissociated to form a suspension of multipotent neural stem cell progeny. These cells can be transplanted, or placed into fresh growth-factor containing culture medium to form secondary cultures (which comprise suspensions of multipotent neural stem cell progeny). The passaging of the cells from the primary culture to the secondary culture is depicted in step **B** of the diagram. In the continued presence of a growth factor, the multipotent neural stem cells of the secondary culture further proliferate **(C)** to form new neurospheres comprised of daughter multipotent neural stem cells and daughter progenitor cells. In contrast, the daughter progenitor cells of the secondary culture are undifferentiated cells that have only a limited ability to proliferate. They may undergo a few divisions **(D)**, but they will not proliferate and form new neurospheres. A progenitor cell is committed to a particular differentiative pathway **(E)**.

Lubetzki *et al.* do not disclose a method for inducing the proliferation of multipotent neural stem cells capable of producing progeny that are capable of differentiating into neurons, astrocytes and oligodendrocytes as recited in applicants' claims. Lubetzki *et al.* were concerned solely with proliferation of glial progenitor cells and oligodendrocytes and state that their cultures were neuron-free (p. 67, middle of page). At the time of the invention, it was known that PDGF induces oligodendrocytes to proliferate

(see p. 41, lines 2-5). PDGF has not been shown to induce neural stem cell proliferation, and thus would not be considered to be a growth factor capable of inducing multipotent neural stem cell proliferation as recited in claim 26. Thus, even if any neural stem cells were present in the cultures of Lubetzki *et al.* (and there is no indication that they were present as the reference state on page 67 under "Cell Cultures" that a Percoll density gradient was used to sort the cells to obtain an oligodendrocyte or O-2A enriched population), there is no reason to believe that they were induced to proliferate, as required by claim 26. Accordingly the Lubetzki *et al.* reference fails to teach every element of the claimed invention and the rejection under § 102 should be withdrawn.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 1-9 under § 103 as being unpatentable over Lubetzki *et al.* in view of Gage *et al.* As claims 1-9 are directed to an unelected invention, it is assumed that the Examiner intended to raise this rejection against claim 27. Applicants respond accordingly.

The Examiner states that Lubetzki *et al.* teach that "nerve cell cultures are obtained from rat brains and expanded using PDGF." However, as indicated above, the cell cultures used by Lubetzki *et al.* were neuron-free ("nerve cell" and neuron) are synonymous terms. In any event, the applicants' methods require the proliferation of multipotent neural stem cells. At the time of Applicants' invention, methods for the proliferation of multipotent neural stem cells, capable of producing progeny that are capable of differentiating into astrocytes, oligodendrocytes and neurons, were not known. Moreover, while PDGF, the growth factor used by Lubetzki *et al.*, is known to induce proliferation of oligodendrocytes, it has not been shown to induce multipotent neural stem cell proliferation. The Gage reference does nothing to cure this deficiency of the Lubetzki

disclosure, as it is concerned with the transplantation of fibroblasts. For these reasons, the rejection under § 103 should be withdrawn.

CONCLUSION

For the foregoing, it is believed that the claims of this application are patentable. Favorable reconsideration is respectfully requested.

Respectfully submitted,

FLEHR, HOHBACH, TEST,
ALBRITTON & HERBERT

Jan P. Brunelle
Reg. No. 35,081

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989

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